

Long-term effect of dipeptidyl peptidase-4 inhibition on β -cell mass in an advanced-aged diet-induced obesity mouse model

Type 2 diabetes is a chronic metabolic disorder characterized by progressive decline of β -cell function and mass. Based on the pathogenesis of the disease, improvement of β -cell function and retention of β -cell mass are crucial targets for treatment of diabetes. A growing body of evidence has shown that incretin-based therapies using glucagon-like peptide 1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors improve insulin secretion and decrease blood glucose levels in both type 2 diabetic patients and animal models of diabetes. Furthermore, multiple studies using rodent models of diabetes have shown that mice treated with GLP-1 receptor agonists and DPP-4 inhibitors can retain β -cell mass, through increasing β -cell proliferation and inhibiting β -cell apoptosis. However, the majority of positive preclinical experiments were carried out using young rodents (<10-weeks-old at the start of the study) or in rodents treated for a short period (<20 weeks) in relation to their lifespan.

In contrast, it has been reported that the proliferative response to multiple regenerative stimuli, including GLP-1 receptor agonists in older rodent β -cells, is seriously impaired (Figure 1)¹. In addition, human β -cells appear to be much less responsive to proliferative agents, such as GLP-1, compared with rodent β -cells², and β -cell replication is almost absent in older human subjects³. Therefore, the term of therapy and the use of younger animals are critical limitations of previous rodent studies with regard to

the effects of incretin-based treatments on β -cell function and mass.

Recently, Omar *et al.*⁴ evaluated the effects of long-term therapy (11 months) with the DPP-4 inhibitor, vildagliptin, on β -cell function and mass in advanced-aged diet-induced obese (DIO) mice (10-months-old at study start), in order to more closely mimic the age of onset of hyperglycemia in human individuals with type 2 diabetes. In that study, they found that chronic treatment with vildagliptin in an advanced-aged DIO model improves insulin secretion in response to oral glucose load throughout the course of the long study period of 11 months. They also reported that, even with extensive long-term therapy with vildagliptin, the β -cell area was not significantly increased, notwithstanding the improvement in β -cell function. However, the study of Omar *et al.*⁴ did not carry out control experiments using young DIO mice. In fact, there is no report showing

that DPP-4 inhibitors or GLP-1 receptor agonists increase β -cell mass in young DIO mice. To the contrary, BOC5, a non-peptidic GLP-1 receptor agonist, reduced the expansion of β -cell mass in DIO mice, probably through attenuated insulin demand resulting from decreased bodyweight.

Butler *et al.*⁵ reported that β -cell mass is decreased in both lean and obese type 2 diabetic human subjects, and that the mechanism underlying decreased β -cell mass is increased β -cell apoptosis. Advanced-aged DIO mice used in the study of Omar *et al.*⁴ showed neither an increase nor decrease in β -cell area compared with normal-diet mice regardless of treatment with vildagliptin. Thus, the advanced-aged high-fat diet (HFD)-fed mouse model differs from human type 2 diabetic patients in the lack of reduced β -cell mass. Zhang *et al.*⁶ showed that chronic administration of alogliptin facilitates restoration of β -cell mass after

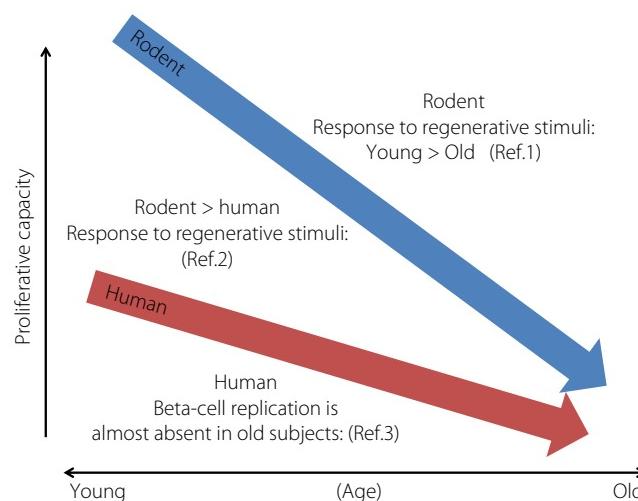


Figure 1 | The proliferative capacity of β -cells is far higher in young rodents that generally have been used to evaluate the effect of incretin-based treatment, compared with that in older human subjects.

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streptozotocin treatment in HFD-fed mice. Thus, we cannot exclude the possibility that incretin-based therapy could exert a proliferative effect on β -cells in the condition of decreased β -cell mass.

There is no direct evidence in humans that incretin-based therapy, including DPP-4 inhibition, leads to increased β -cell mass. However, some clinical data shows the possibility of β -cell retention or expansion by incretin enhancement. Scherbaum *et al.*⁷ showed that 2-year treatment with vildagliptin maintains the improved parameters of insulin secretion even after 4-week drug cessation in patients with type 2 diabetes. Similarly, after 3-year treatment of type 2 diabetic patients with exenatide, the parameter of insulin secretion was sustained after a 4-week off-drug period. These data might suggest a protective effect of vildagliptin and exenatide against progressive decline in β -cell mass in type 2 diabetes. Furthermore, some patients who have undergone Roux-en-Y gastric bypass for treatment of extreme obesity show post-prandial hyperinsulinemia and nesidioblastosis associated with a high serum GLP-1 concentration, possibly owing to the rapid presentation of nutrients to the distal ileum, the site of GLP-1-producing L cells. Increased levels of GLP-1 could contribute to the hypertrophy of pancreatic β -cells in these patients.

Considered together, based on the results of the study using HFD-fed advanced-aged mice, the stimulatory

effect of vildagliptin on β -cell proliferation would seem to be limited in elderly subjects. However, as aforementioned, even advanced-aged DIO mice do not completely mimic the natural development of human type 2 diabetes. A method for accurate and non-invasive assessment of functional β -cell mass *in vivo* is required to monitor the impact of incretin-based therapies on β -cell mass in human diabetes.

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